NCT03396926

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Phase II Study of Pembrolizumab Plus Capecitabine and Bevacizumab in Microsatellite Stable Metastatic Colorectal Cancer.

This is a clinical trial, a type of research study. Your study doctor, Chloe E. Atreya MD, PhD, or one of her associates from the UCSF Helen Diller Family Comprehensive Cancer Center, will explain this study to you.

Clinical trials include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this research study because you have metastatic or advanced colorectal cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out how safe pembrolizumab is in combination with capecitabine and bevacizumab and also to see what effects, good and/or bad, this combination has on your colorectal cancer.

Pembrolizumab is an antibody that is designed to bind to and block the activity of PD-1, a molecule in your body that may be responsible for inhibiting your body's immune response against your cancer cells. The use of pembrolizumab in this study is experimental. This means pembrolizumab is not approved for the treatment of your cancer by the US Food and Drug Administration (FDA).

Capecitabine (also known as Xeloda) is approved by the FDA for treating colorectal cancer. The rationale for combining capecitabine with pembrolizumab is that capecitabine has been shown to stimulate the immune system, which may improve effects of pembrolizumab. The combination of capecitabine with pembrolizumab has been tested in patients with rectal, breast, and gastroesophageal cancers; no unexpected toxicities have been reported with this combination.

Bevacizumab (also known as Avastin) is approved by the FDA for treating colorectal cancer. The rationale for combining bevacizumab with pembrolizumab is that bevacizumab has been shown to reduce the immunosuppressive features of tumors and increase immune cell infiltration into tumors. The combination of bevacizumab with pembrolizumab has been tested in patients with kidney, brain, skin, and lung cancers; no unexpected toxicities have been reported with this combination.

The combination of pembrolizumab plus capecitabine and bevacizumab has not been tested in patients with colorectal cancer or other tumor types.

Merck Sharp & Dohme Corporation, which manufactures pembrolizumab, is supplying the study drug free of charge and providing funding for the study. Capecitabine and bevacizumab are standard of care therapies for metastatic colorectal cancer and will be billed to you or your insurer.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study plans to enroll and treat about 50 people at UCSF.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you consent and are eligible to participate in this study, you will be enrolled in one of two phases. Your study doctor will tell you which phase you are in, and what drug doses you will be receiving.

In the first phase:

The purpose of the first phase is to see what the best dose of capecitabine is when used with pembrolizumab and bevacizumab.

Three patients will be treated with full-dose pembrolizumab, bevacizumab, and capecitabine for 1 treatment cycle (3 weeks; each cycle is 21 days). If 2 or more of these patients don't have any serious unexpected side effects, another 3 patients will be enrolled, treated at the same dose, and followed for 3 weeks. If 5 or more of these patients don't experience any serious side effects, then this dose of capecitabine will be considered the best dose and will be used for the rest of the study. If, however, 2 or more patients experience serious side effects, then the capecitabine dose will be reduced.

In the second phase:

About 40 patients will receive pembrolizumab plus capecitabine and bevacizumab at the dose determined in the first phase of the study.

The first 23 patients enrolled in the second phase of this study will have a tumor biopsy before starting treatment and will also have a second biopsy in the middle of the first cycle (if it is safe to do so). Because bevacizumab increases the risk of bleeding during biopsy, the first 23 patients enrolled in the second phase will receive capecitabine plus pembrolizumab (without bevacizumab) during the first cycle. Bevacizumab will be added to capecitabine and pembrolizumab starting in the second cycle, after the biopsies. These biopsies are to look at how your immune system reacts to the drugs and are for research purposes only. By consenting to participate in this study, you are agreeing to the possibility of undergoing two biopsies.

If you are enrolling into the second phase of this study, after 23 patients have already enrolled, your study doctor will let you know whether or not you will have a biopsy before starting treatment. If not enough biopsy samples were collected from the first 23 patients enrolled in the second phase, then additional participants will have a biopsy done before starting treatment (if it is safe to do so) until enough biopsy samples are collected for the study. A second biopsy, in the middle of the first cycle, will not be requested. Bevacizumab will be added to capecitabine and pembrolizumab starting in the first cycle.

BEFORE YOU BEGIN THE MAIN PART OF THE STUDY...

Screening

You will need to have the following exams, tests, or procedures to find out if you can be in the main part of the study. Some of these exams, tests, or procedures are part of routine cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

All procedures must be done within 28 days prior to the start of the treatment unless otherwise noted. The Screening Visit may take approximately 4-5 hours to complete.

- Medical history review – You will be asked about your health, any current and past illnesses. You will also be asked about previous treatments you have received for your cancer.
- Questions about how well you are functioning in day-to-day life
- Medication review (medications that you happen to be taking in addition to the study drug)
- Physical exam, including measurements of vital signs and weight
- Blood (about 5 tablespoons) will be drawn for tests including:
    - Complete blood count
    - Blood chemistry
    - How fast your blood clots
    - Tumor markers
    - Thyroid tests
    - Presence and activity of T-cells and other immune cells
    - The DNA sequence of your T-cells
- Urinalysis
- Pregnancy testing – if you are a woman of childbearing potential you will have a pregnancy test (blood or urine) within 72 hours before your first dose of treatment
- Tumor assessment preferably by a computed tomography (CT) scan of the thorax, abdomen, and pelvis; or Magnetic Resonance Imaging (MRI)
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line that is attached to a needle in your arm and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
    - An MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special

dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the radiology department and takes approximately an hour and a half to complete.

- Electrocardiogram (ECG). The ECG checks the function of your heart by recording the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. This takes about 15-30 minutes.
- An archival sample of your tumor (one collected during a previous biopsy or surgery) will be collected if available. These samples are being collected for biomarker testing and will include:
    - Tests for PD-L1 protein expression
    - Examination of the immune cells associated with your tumor including DNA sequencing (testing the genes) of your immune cells and/or of your tumor.
- Tumor biopsy: if you are enrolled in the second phase of the study, you may be asked to provide a sample of your tumor through a biopsy before the first dose of study drugs (after you have passed through the rest of screening).
    - The first 23 patients enrolled in the second phase of this study will have a tumor biopsy before the first dose of study drugs, as long as it is safe to do so. After 23 patients are enrolled in the second phase, if not enough samples have been collected for the study, additional patients will have biopsies performed before receiving study drugs. Your study doctor will let you know whether or not you will have a biopsy before starting the study drugs.
    - A biopsy is an outpatient procedure to remove a piece of your tumor tissue using a special needle. This procedure will be done at the site where we can most easily get a piece of the tumor and can involve the lungs, liver, bone, lymph node, skin, or other. The biopsy needle will be inserted into tumor tissue and a small piece of tumor will be removed. 1-3 passes with this needle will be made. The needle may be guided by a CT or ultrasound (US). The biopsy will help us understand more about the disease, how pembrolizumab, capecitabine, and bevacizumab work together, and the biomarkers which are involved. These biomarkers may include genes (DNA and RNA) or proteins and immune cells. Part of your biopsy sample may also be used to create tumor models in animals for research. This procedure takes about 30 minutes.

DURING THE MAIN PART OF THE STUDY...

If the exams, tests, and procedures show that you can be in the main part of the study, and you choose to take part, then you will need the following tests and procedures. Some of them are part of routine cancer care and may not need to be repeated if you have had them done recently. This will be up to your study doctor. Visits will take about 2-6 hours to complete.

You will also receive treatment with the study drugs pembrolizumab, capecitabine, and bevacizumab.

Study Treatment:

You will receive pembrolizumab by infusion on the first day (day 1) of every 21-day (3 weeks) treatment cycle.

If you are enrolled in the first phase of the study, you will also receive bevacizumab by infusion on the first day (day 1) of every 21-day (3 weeks) treatment cycle. Additionally, you will be instructed to take capecitabine pills by mouth twice daily for 14 days out of each 21-day cycle.

If you are one of the first 23 patients enrolled in the second phase of the study, you will be instructed to take capecitabine pills by mouth twice daily for 14 days out of each 21-day cycle. Bevacizumab will be administered by infusion on the first day (day 1) of every 21-day (3 weeks) treatment cycle starting with cycle 2 (bevacizumab will not be administered the first treatment cycle for the first 23 patients enrolled during the second phase of the study).

If you are enrolled in the second phase, after 23 patients have enrolled in the second phase, you will be instructed to take capecitabine pills by mouth twice daily for 14 days out of each 21-day cycle. Bevacizumab will be administered by infusion on the first day (day 1) of every 21-day (3 weeks) treatment cycle starting with cycle 1.

You will be given a drug diary to record capecitabine dosing.

During the treatment, your doctor will be monitoring how the study drugs affect your cancer and your overall health. To track these effects, you will have a CT scan and/or MRI approximately every 9 weeks; a urinalysis and blood tests for cell counts, chemistry testing, and the tumor marker test approximately every 3 weeks; and blood tests for thyroid function approximately every 6 weeks.

Other tests and procedures will occur during your scheduled visits to the clinic:

Cycle 1, Day 1 (some procedures will be done before your dose of the study drug)

- Physical exam, including measurements of vital signs and weight
- Blood (about 7-9 tablespoons) will be drawn for routine and research tests
- Pregnancy testing (blood or urine) – if you are a woman of childbearing potential
- Urinalysis
- Evaluation of symptoms
- Medication review
- Administration of the study drug, pembrolizumab via infusion (a needle in your arm or chest port)
- First phase *and* after 23 patients enroll in the second phase: administration of bevacizumab via infusion (a needle in your arm or chest port)
- Initiate oral capecitabine with evening meal (to be taken twice daily on days 1-14 of each treatment cycle)

Cycle 1, Day 14 (approximate)

First 23 participants of Second Phase only

- Tumor biopsy: Patients with a pre-treatment biopsy that was confirmed to contain tumor, and in whom repeat biopsy is determined by the study team to be feasible and not associated with excessively high procedural risk, will be asked to undergo a second tumor biopsy in the middle of Cycle 1 to assess for changes to the tumor-induced by the study medications.

Cycle 2 and 3, Day 1

- Physical exam, including measurements of vital signs and weight
- Blood (about 7-9 tablespoons) will be drawn for routine and research tests
- Pregnancy testing (blood or urine) – if you are a woman of childbearing potential
- Urinalysis
- Evaluation of adverse events (any side effects you may be experiencing)
- Medication review
- Administration of the study drug, pembrolizumab via infusion (a needle in your arm or chest port)
- Administration of bevacizumab via infusion (a needle in your arm or chest port)
- Initiate oral capecitabine with evening meal (to be taken twice daily on days 1-14 of each treatment cycle)

Cycle 4 and Future Cycles, Day 1

- Physical exam, including measurements of vital signs and weight
- Blood (about 6-8 tablespoons) will be drawn for routine and research tests
- Pregnancy testing – if you are a woman of childbearing potential
- Urinalysis
- Evaluation of adverse events (any side effects you may be experiencing)
- Medication review
- Administration of the study drug, pembrolizumab via infusion (a needle in your arm or chest port)
- Administration of bevacizumab via infusion (a needle in your arm or chest port)
- Initiate oral capecitabine with evening meal (to be taken twice daily on days 1-14 of each treatment cycle)
- Tumor imaging assessments by CT scan of the thorax, abdomen, and pelvis (preferred) or MRI will be performed approximately every 9 weeks, starting from the date of the first dose of study drugs, or earlier if clinically indicated.

End of Treatment Visit

After you take the final dose of the study drugs, you will be asked to come to the clinic for an end of study visit. At this visit, you will have the following procedures done. The visit will take approximately 2 hours.

- Physical exam, including measurements of vital signs and weight
- Blood (about 6-8 tablespoons) will be drawn for routine and research tests
- Pregnancy testing – if you are a woman of childbearing potential
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- Evaluation of adverse events (any side effects you may be experiencing)
- Medication review
- Tumor imaging assessments by CT scan of the thorax, abdomen, and pelvis (preferred) or MRI

Safety Follow-up Visit

A Safety Follow-up Visit will be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

- Blood (about 1-3 tablespoons) will be drawn for routine tests
- Pregnancy testing – if you are a woman of childbearing potential
- Urinalysis
- Evaluation of adverse events (any side effects you may be experiencing)
- Medication review

Discontinuation of the Clinical Trial

If you decide to stop being part of the study, or you need to withdraw because of side effects, and you have not had growth in your tumor/s, you will have CT scans every 9 weeks until your cancer gets worse. If you stop participating in the study because your cancer got worse, you will not have these scans as part of this study but will need to follow up with your doctor or other provider to decide on the next treatment for your cancer. You will also be contacted over the telephone every 9 weeks for as long as possible, or until you withdraw your consent, or the study ends.

Study location: All doctor's visits or nurse visits, research blood draws, and pembrolizumab and bevacizumab infusions will be done at the UCSF Helen Diller Family Comprehensive Cancer Center. You may have some of the standard blood draws, CT scans, and/or MRI scans performed at another facility if needed or at UCSF. Telephone follow up visits may be performed at some of the visit time-points if your study doctor determines this is appropriate for your case.

HOW LONG WILL I BE IN THE STUDY?

The length of the study will be different for each patient. We think you will be on the study for at least 63 days (Cycles 1 to 3). If there are no severe side effects and if your cancer has not gotten worse, you may receive additional treatment cycles with the same dose of the study drug

pembrolizumab for up to 35 treatments, or two years, whichever is longer. If, on the other hand, you experience severe side effects from the study drug, you may be asked to stop the treatment or receive a lower dose of capecitabine. If it is clear your cancer is getting worse while receiving the study drug, you may be instructed by your study doctor to stop taking the study drug.

The study doctor may decide to take you off the research study for other various reasons, including:

- If you have had a very good response to treatment without any sign of tumor growth and no bad side effects after 35 treatments of pembrolizumab or 24 months, whichever is longer
- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with study treatments and procedures
- There are any problems with research funding or study drug supply;

There may be other reasons that you stop receiving the study drug. Your study doctor will discuss this with you.

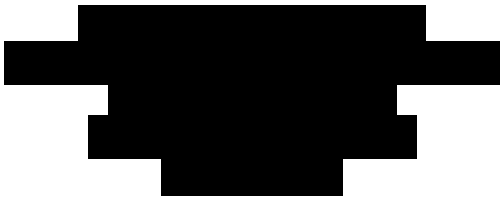
CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. S/he will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest (such as if you have severe side effects), if you do not follow the study rules, or if the study is stopped.

You can stop participating in the research study at any time. However, before you decide to stop participating in this research study, we encourage you to talk to the research study doctor and your regular doctor first. **Please note that even if you wish to stop study treatments for any reason, your progress may continue to be followed through your medical records for safety reasons and to monitor your long-term cancer and health outcomes, unless you specifically request in writing (to the address below) that access to your records be limited.**



WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking pembrolizumab, capecitabine, and/or bevacizumab. In some cases, side effects can be serious, long-lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Risks and side effects related to the pembrolizumab include those which are:

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very common side effects (some may be serious) seen in 20% or more of patients treated with pembrolizumab include the following:

- Itching of the skin
- Loose or watery stools
- Cough

Common side effects (some may be serious) seen in 5% to less than 20% of patients treated with pembrolizumab include the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

Uncommon side effects (some may be serious) seen in 1% to less than 5% of patients treated with pembrolizumab include the following:

- Inflammation of the lungs so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching, and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body, which can cause severe infection (severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis)

Rare side effects (some may be serious) seen in less than 1% of patients treated with pembrolizumab include the following:

- Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upper body, leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting, and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)

- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney, so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)

Additionally, since pembrolizumab was approved (for melanoma) in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness, and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin, and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin, and hearing loss (Vogt-Koyanagi-Harada syndrome)

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

In addition to what is specifically listed above, drugs that help stimulate the body's immune response against tumor cells (immunotherapy drugs), such as pembrolizumab, may cause severe inflammation to every organ.

Risks and side effects related to Capecitabine include those which are:

Very common. Out of 100 people who receive capecitabine, 20 or more people with colorectal cancer may have the following:

- Diarrhea
- Sores in mouth and throat that may make swallowing difficult and painful
- Nausea
- Vomiting
- Pain in your stomach or abdomen
- Palms of your hands or soles of your feet tingle, become numb, painful, swollen, or red (called "hand-foot syndrome")
- Dry or itchy skin
- Skin rash
- Feeling tired and weak
- Reduced appetite
- Low levels of red blood cells
- Increased levels of bilirubin in the blood (a pigment in the blood)

Common. Out of 100 people who receive capecitabine, at least 5 but less than 20 people with colorectal cancer may have the following:

- Constipation
- Drop in number of a type of white blood cells. You may be more likely to get infections.
- Heartburn
- Hair loss
- Red or sore eyes
- Vision changes
- Fever
- Dizziness
- Headache

- Pain, including joint, muscle, bone, back, or chest pain
- Infection
- Swelling in your arms or legs
- Reduced feeling in your hands and feet
- Bleeding in your stomach or intestines
- Blockage or slowing of your intestines
- Changes in your skin color
- Depression or feeling changes in your mood
- Shortness of breath
-

Rare but Serious. Out of 100 people who receive capecitabine, less than 5 people with colorectal cancer may have the following:

- Blood clots and/or bleeding
- Severe water loss in the body (called dehydration) which may require you to stay in a hospital. Dehydration can also cause injury to your kidneys (usually temporary).
- Abnormal liver function test-blood tests which may mean your liver is not working properly or liver failure
- Heart attack
- Abnormal heart rhythm (called arrhythmia)

There may be other side effects that could occur.

Risks and side effects related to Bevacizumab include those which are:

Very common side effects seen frequently in patients treated with bevacizumab include the following:

- A feeling of weakness and/or tiredness
- Nausea, vomiting, or loss of appetite
- Headache
- Bloody nose
- Shortness of breath
- Infections
- High blood pressure
- Diarrhea or Constipation
- Aches and pains in the muscles and joints
- Protein in the urine which may indicate kidney damage
- Low white blood count in combination with other chemotherapy drugs
- Runny nose, sneezing, and/or an infection in your sinuses
- Dry mouth or taste changes
- Watery eyes
- Dry skin
- Rectal bleeding

- Skin changes such as rashes, hives, skin sores

Common to less common side effects seen occasionally in patients treated with bevacizumab include the following:

- Acid or upset stomach (heartburn)
- Loss of weight
- Hoarseness or other change in voice
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)
- Feelings of dizziness or fainting, drowsiness, or depression
- Hair loss
- Fever, chills including shaking chill
- Pain in the chest, back, or abdomen (belly)
- Low number of red and white blood cells which might require red cell transfusion and higher risk of infections
- Low number of platelets which might lead to bleeding
- Urinary tract infection
- An ulcer in your stomach or intestines
- Bleeding from your stomach or intestines
- A hole in the wall between the two sides of your nose
- Changes in how the body forms clots, stops bleeding, and heals wounds. This may result in clots forming when they should not which can lead to pain and swelling in the area of the clot or may be life-threatening if they form in the heart or brain (usually only seen in elderly people). Such clots may also break loose and cause damage or be life-threatening depending on where they go. This may also result in poor wound healing after surgery or trauma or bleeding from areas such as the intestines.
- Numbness and tingling in the fingers and toes and/or increased sensitivity to feeling such as touch or pain
- Low blood pressure

Rare but Serious side effects seen rarely in patients treated with bevacizumab include the following:

- Severe allergic reactions with the infusion including shortness of breath, wheezing, a very high blood pressure, chills, sweating, chest pain, and a headache
- Severe rashes which can result in loss of skin and damage to the tissues that line body cavities such as the mouth and throat and the intestines.
- Severe bleeding which can occur in the head, lungs, stools, urine, and other parts of the body and which may be life-threatening
- Inflammation of the part of the intestines known as the colon which can lead to infection, blood in the stools, and abdominal (belly) pain
- Rupture of the bowel that causes the contents of the bowel to spill into the abdominal cavity
- Blockage of the intestines
- Damage to the brain which may lead to difficulty thinking, carrying out normal tasks,

seizures (convulsions), difficulty seeing, blindness, or other visual changes, which if caught early can be reversed
- If you take Bevacizumab with chemotherapy you might get a serious infection that may lead to death
- Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid
- Kidney damage or failure
- A hole in the between your windpipe (trachea) and your swallowing passage (esophagus); this usually happens when you also get radiation to this area
- Blood clots in the arteries which can block the blood flow to such areas as the brain leading to strokes, the heart with possible heart attack, the intestines, or the legs. The lack of blood flow can damage these organs or be life-threatening. These are more common in older people with pre-existing problems such as heart or blood vessel disease.
- A re-opening of a wound along the surgical suture lines
- Death of tumor cells causing damage to healthy tissue in the area of the tumor which may result in a puncture in the lining of the lungs and bleeding which may be life-threatening

There may be other side effects that could occur.

Risks and side effects related to the study procedures

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.
- **Biopsy risks:** The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure can be unsuccessful and require a repeat biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

- **Electrocardiogram (ECG):** ECGs are electrical tracings of the heartbeat or heart rhythm in which you will have pads placed on different parts of your body. The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

- **Infusion risks:** As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter

(small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.

- **Study Drug Combination:** The side effects of pembrolizumab in combination with capecitabine and bevacizumab are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug-related effects.

- **Radiation risks:** This research study involves exposure to a significant amount of radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. The additional amount of radiation that you will receive as a result of participating in this study will be a maximum of approximately 50 mSv, which is equivalent to slightly less than 17 times the yearly natural background of radiation in the US, which is 3 mSv (an mSv, or milliSievert, is a measurement of radiation). This amount of radiation involves a low, lifetime risk of cancer. However, the UCSF Radiation Safety Committee has reviewed the use of radiation in this research study and has designated this use as acceptable to obtain the benefits provided by the results of the study. If you are pregnant, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

- **CT scan risks:** CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.

  Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting, or a headache.

- **MRI risks:** Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocketknives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear earplugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

- **Contrast agent (gadolinium) risks**: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

  Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have an MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

- **Confidentiality Risks:** There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe this risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job.

- **Genetic Testing Confidentiality Risks:** There is a risk someone could get access to the genetic information in your medical records. Even without your name or other identifiers, your genetic information is unique to you, like a fingerprint. Someone might be able to trace this information back to you. In some cases, this information could be used to make it harder for you to get or keep a job. The laws against misuse of genetic information give limited protection. We cannot guarantee complete privacy.

- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study could affect an unborn baby or your fertility or ability to become pregnant. If you are a woman and become pregnant after receiving the study drug or are male and your partner becomes pregnant during the study, you must notify the study doctor right away. Women should not breastfeed a baby while in this study. It is important to understand that you need to use birth control while on this study and for at least 120 days after your last dose of the study drug. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

    - **Female patients** of childbearing potential should have a negative urine or serum

pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Female patients should be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.

Male patients should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

- **Dose Risks:** Patients may be assigned to different doses of capecitabine during the first phase of the study. Some patients may receive a higher dose of the drug that may cause increased side effects, while others may receive a dose of the drug that is too small to be effective. You can ask your study doctor what dose you will be given.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope pembrolizumab, capecitabine, and bevacizumab will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about the combination of these drugs as a treatment for cancer. This information could help future cancer patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

HOW WILL MY SPECIMENS AND INFORMATION BE USED?

Researchers will use your blood and tissue specimens and information to conduct this study. Once the study is done using your specimens and information, we may share them with other researchers so they can use them for other cancer studies in the future. We will not share your name or any other personal information that would let the researchers know who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Your blood and tissue specimens will be stored in a repository, also called a 'tissue bank', at UCSF. The manager of tissue bank and select tissue bank staff members will have access to your specimens and information about you, but they will not release any identifying information about you to researchers using your specimens. We may give your specimens and certain medical information about you (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies not at UCSF, including to an unrestricted or controlled-access government health research database, but we will not give them your name, address, phone number, or any other identifiable information. Your specimens and information will be kept indefinitely until they are used up or destroyed.

Research results from these studies will not be returned to you and will not be put in your medical record. The research will not change the care you receive.

Researchers may use your blood and tissue specimens to look at all of your DNA (this is called "whole genome sequencing"). DNA contains information that determines things like eye color, height, or disease risk that are passed on from parent to child. Genetic information (also known as genotype data) and the medical record data (also known as phenotype data) may be shared broadly in a coded form for future genetic research or analysis.

Donating data and specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. It is possible that future research could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

There will be no direct benefit to you from allowing your specimens and data to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease. If your specimens, the data or any new products, tests or discoveries that result from this research have potential commercial value, you will not share in any financial benefits.

If you decide later that you do not want your information to be used for future research, you can notify the investigator in writing [redacted]

[redacted]

and any remaining specimens and data will be destroyed. However, we cannot retract any specimens and data that has been shared with other researchers.

HOW WILL INFORMATION ABOUT ME BE KEPT CONFIDENTIAL?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you.

Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and any information added to your medical record as a result of your participation.

Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records and may be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis or analyze your blood or tumor samples include:

- Merck Sharp & Dohme Corporation
- The University of California
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

In order to allow the greatest amount of research to be performed on the specimens you donate and learn the greatest amount possible, researchers for this study may share your tissue, blood, and de-identified medical information with other scientists and researchers at other universities, government, hospitals, health-related companies or research institutions.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Merck Sharp & Dohme Corporation is supplying pembrolizumab at no cost to you.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs

if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

Before you agree to be in this study, you may want to contact your healthcare payer/insurer to see if your plan will cover the costs required as part of your participation. You may request more information about the costs of participating in this study and discuss this with the study team.

If you have any questions, your doctor and the study team will be able to provide you with answers.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, Chloe E. Atreya, MD, PhD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call her [redacted]

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the UCSF Institutional Review Board (IRB) at 415-476-1814.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Chloe E. Atreya, MD, PhD, [redacted].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the UCSF Institutional Review Board (IRB) at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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OPTIONAL RESEARCH

Please note: This section of the informed consent form is about additional research studies that are being done using leftover or "extra" blood and tumor samples after the main research has been completed. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Tissue and Blood for Future Research

You may undergo surgical procedures during your participation in this study at baseline, and at subsequent time points during and after study treatment, that are a part of your routine care. If available, archived tissue from these routine surgical procedures will be collected for this research. In addition, blood for this research will be collected at baseline, during study treatment, and at the end of treatment.

After all of the tests for this research are complete, and if there are any leftover research blood and archival tissue, we would like to keep them for future research. Future research may include testing for immunologic and genomic biomarkers related to colorectal cancers.

There will be no direct benefit to you from allowing your specimens to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease.

Results from this analysis may be published but your data will not be reported individually. Reports about research done with your leftover specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep specimens for future research is optional and is up to you. No matter what you decide to do, it will not affect your care.

Your tissue and blood specimen will be stored in a repository at UCSF. If you decide now that your specimens can be kept for future research, you can change your mind at any time. Just contact the study doctor, Chloe E. Atreya, MD, PhD, in writing at the address below, and let us know that you do not want us to keep your specimens.

[redacted]

[redacted]

Any identifiable specimen that remains will no longer be used for research and destroyed. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

In the future, people who do research may need to know more about your health. While the study doctor may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimen will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future. You will not be paid for allowing your tumor samples to be used in research even though the research done with your samples may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from these samples.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

Risks include a loss of privacy as previously discussed on page 16, **Confidentiality**.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence put your initials in the "Yes", or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care.

1. Any leftover tumor samples or materials from any biopsy and/or surgeries I have had for my cancer can be stored for future research including genetic testing related to colorectal cancers.

YES	NO

2. Any leftover blood samples collected for this clinical trial may be kept for future research including genetic testing related to colorectal cancers.

YES	NO

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CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent
Date	Witness – Only required if the participant is a non-English speaker